U.S. Food and Drug Administration
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Pet Peeves and Roadblocks in CMC: Improving your Quality Submissions through the Product Lifecycle

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FDA Small Business Regulatory Education for Industry Conference
June 19, 2013

Disclaimer

- This presentation does not represent official FDA policy.
- However, it represents the opinions of most of the reviewers in OBP.
- So, it may be more important than official FDA policy!
  - (Just kidding!)

Objectives

- Take home messages and Pet Peeves
- Roadblocks
  - Basics
  - Phase 1
  - Phase 2/3
  - BLA
- Breakthrough Therapy Designation
- Biosimilars

Take Home Message #1

A grumpy reviewer is <u>not</u> your best friend!!!!!

Volcanic Eruptions Around the World

Mt. Eyjafjallajokull, Iceland

Arenal, Costa Rica

Marjie, Bethesda Maryland

Tungura

Overarching Pet Peeves

- Inefficient use of reviewer time
  - While you might like to believe that a reviewer is assigned to only one IND – yours, this is pure fantasy!
- Poor communication

"It cost $1299. But when you factor in the time wasted sitting in front of it, well, the real cost is enormous."

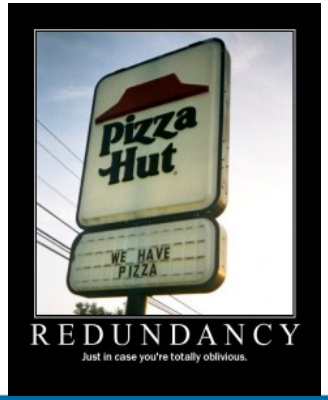
The cost can be enormous, and not just in $$, if your submission is confusing

Pet Peeve #1 - CTD format

- It's redundant!
  - Duplication of information within a submission
- It's redundant!
  - Duplication of information in subsequent submissions (amendments or new INDs)
  - Inefficient use of reviewer time
- It's not organized in a manner that tells the whole story in a logical manner

Pet Peeve #1 - CTD format

- It can be hard to find specific information
- It's small drug centric. Make it work for biologics
  - $C_{10,000}$, $H_{50,000}$, O_{5000}, S_{16}
- It's redundant!
  - (Did I already say that?)



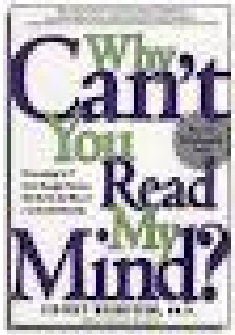
CTD Format

- Do
  - Learn to live with CTD format but
    - Try to make it as non-repetitive as possible
  - Provide sufficient information
  - Present information that is well organized and clear
  - Links to other sections should work
  - Module 2 is for a summary
  - Proofread! Proofread! Proofread!
- Don't
  - Assume it is obvious what you mean – especially if you haven't proofread the submission.

Pet Peeve #2

Poor Communication with FDA

- $#!+ Happens!
- Incomplete details
- Poorly written submission
- Lack of appropriate meetings with FDA to discuss quality issues



Poor Communication

Poor Communication with FDA $#!+ Happens!

- Do
  - Be honest! It's not what happens, it's how you handle it! (most of the time!)
  - Share information and results of investigations.
- Don't
  - Tell partial story.
  - Come back 2 years later with the whole story.

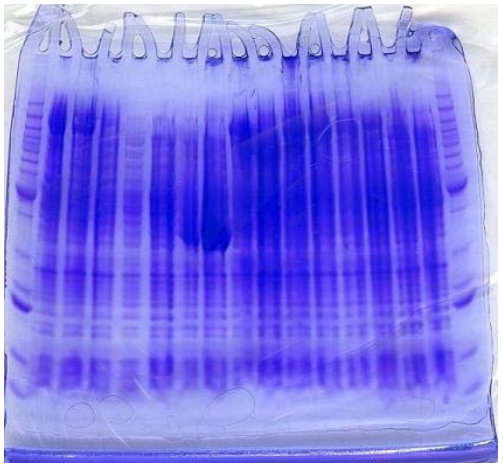
Poor Communication with FDA

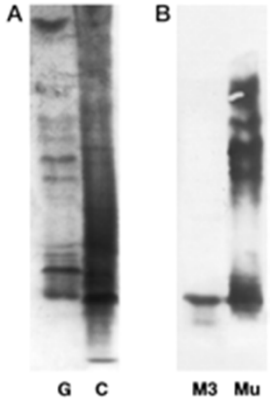
- Do
  - Proofread submissions
  - Ask focused questions at pre-IND, EOP2, pre-BLA meetings
- Don't
  - Submit poorly written documents
  - Ask too general or overly ambitious questions at meetings

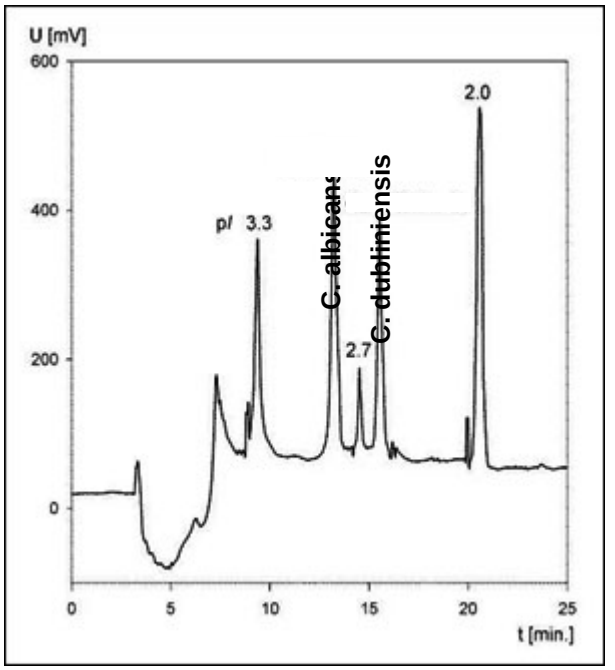
Pet Peeve #3
Data Presentation

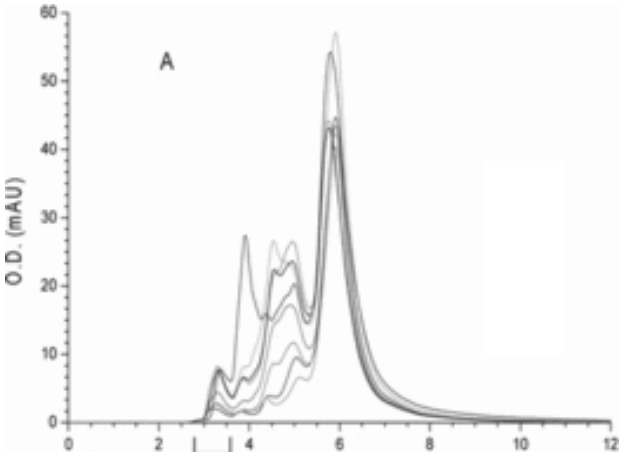
- We're scientists – we like to analyze data
- Missing data
- Poor quality figures
- Confusing tables

Poor Quality Figures









Data Presentation

- Do
  - Pay attention to details
  - Label clearly
  - Lay out in a way that makes it easy to compare peaks, bands etc
  - Include figure legends
- Don't
  - Place text over peaks, especially if the reviewer will be comparing peaks between chromatograms of different lots.
  - Put figures that reviewer will compare on different pages.

Pet Peeve #4

Repeating Mistakes

- Lack of understanding of quality issues at specific phases of clinical development
- Apparent lack of understanding or a disregard of FDA advice

Repeating Mistakes

- Do
  - Show you take our advice into consideration
  - Ask for clarification if you are not sure what we are asking
  - Provide a risk analysis and/or scientific data for a different approach
  - Understand quality issues for phase 1 versus phase 2/3 and BLA
- Don't
  - Ignore FDA comments or advice
  - Marginalize quality concerns

Pet Peeve #5

Poor communication within your company

- Small company with one location
- Large company with multiple sites
- Know your fellow product development colleagues

Poor communication within your company

- Do
  - Share comments from FDA with groups for whom the comment was intended.
  - Share comments from FDA with colleagues in product development associated with different clinical indications.
  - Show you can learn from our comments.
- Don't
  - File the FDA letter without sharing comments with relevant departments
  - Submit subsequent amendments or INDs with same lack of information. You are guaranteed to get the same comments.

Pet Peeve #6

Back up your claims with data

- Your product may be the greatest invention since sliced bread, but we need to come to the same conclusion (and we might not!).
- Protein engineering should accomplish what it was intended to do.

Back up your claims with data

- Do
  - Provide data demonstrating your claim
  - Provide data demonstrating the engineered protein does what the engineering was supposed to achieve
- Don't
  - Hand wave or market to your reviewer
  - Assume your reviewer automatically agrees with your claim

Take Home Message #2

It's not style over substance, but rather it is substance with style!!!!

A complete, well organized, well written submission full of clear figures and tables goes a long way towards making the life of your reviewer a little bit easier.

Take Home Message #3

Trust is an important component of the regulator-sponsor relationship, but it must be earned. Ignoring our advice without a discussion or being less than truthful does not build trust!

Get ready for specific pet peeves and roadblocks…..

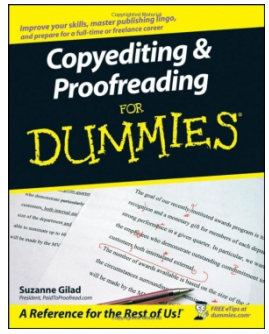
The basics: Understand your audience, identify your needs

- The cover-letter - include relevant items for directing the submission to the appropriate review groups **(Pet Peeve #2 Poor Communication with FDA)**
  - Identify product type is it a biotechnology product? small drug molecule? A combination of both? This will help direct your submission to the appropriate reviewers.
  - Identify what you are submitting AND your needs e.g.
    - Full response vs. partial response to clinical hold
    - Comparability data for which you would prefer feedback by a specific date (be realistic on timelines, provide submission sufficiently early to give ample time for review**. See Overarching Pet Peeves about pure fantasy)**
    - Meeting request – who will you need to be there based on questions to be answered?

The basics: Proofread! Proofread! Proofread!

Don't neglect the QA on the written document.

- Clinical protocol stated product "can be shipped at -20 or above" instead of "at -20ºC to -10ºC". The reviewer had to request that sponsor check and fix all documents with contractors involved in shipping.
- Conflicts: tables list different specifications or results in different sections, or in conflict with the text.
- Don't mistake "regulatorese" for good quality information. Be specific and provide sufficient data for reviewers to make the appropriate conclusions.
- Don't assume the reviewers know what you're talking about.



Take Home Message #2 **Substance with style**
Pet Peeve #2 **Poor communication with FDA**
Pet Peeve #4 **Repeating mistakes**

Meetings: Take full advantage of that rare opportunity to get the best guidance from the FDA.

Examples of missed opportunities at meetings with the FDA

- The data contained in the meeting package is insufficient to answer the questions asked:
  - *"The data package lacks information needed to determine ..."*
  - *"Based on the information provided in the submission package, it cannot be determined whether…"*
- pIND questions that are impossible to answer
  - "*Does the agency agree that the quality data and control strategy would be acceptable for registration?"*

"If you are getting boilerplate answers instead of replies specific to your product, you have not crafted your questions well." **Ruth Cordoba-Rodriguez**

Pet Peeve #2 **Poor communication with FDA**
Pet Peeve #3 **Data Presentation**

Phase 1 – focus on safety

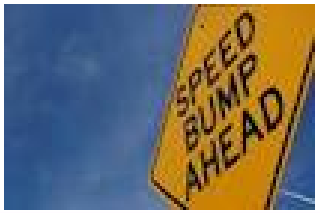
"The identification of a safety concern or insufficient data to make an evaluation of safety is the only basis for a clinical hold based on the CMC section." **(CDER/CBER Guidance for Industry Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products November, 1995)**

- Sterility, mycoplasma, endotoxin, adventitious agents
- Potency (for dosing consistency)
- Identity (prevent confusions at manufacturing site)
- Purity (relevance of non-clinical data etc.)
- Process and product understanding to enable assessment of safety
  - Is non-clinical lot representative of clinical GMP lot?
  - Is this process within the platform process for which virus clearance is claimed?
  - Are acceptance criteria appropriate to assure a meaningful dosing study? Establish provisional preliminary specifications!
  - Is the product sufficiently stable to assure a meaningful dosing study?

Phase 1 Speed Bumps = Clinical Hold

- Your IND is on clinical hold because the subjects in the proposed clinical investigation would be exposed to a **significant and unreasonable risk** [21 CFR 312.42(b)(1)(i)]

- Your IND is on clinical hold because **insufficient information** has been submitted to allow FDA to assess the risks to the subjects in the proposed clinical investigation [21 CFR 312.42(b)(1)(iv)]



Significant and unreasonable risk

- Unacceptable specifications
  - Endotoxin limit > 5 EU/kg/hr, >0.2 EU/kg/hr for intrathecal, or >0.5 EU/mL for intraocular.
  - Potency assay specifications depend on therapeutic index, toxicity, and dosing.
- Evidence of product contamination
- Insufficient virus clearance
- Mislabeled Product

Significant and unreasonable risk

- We note that the maximum dose for this study is Ymg. The current specification for endotoxin content in the drug product is set at X EU/mg which is above the safety limit for the maximum dose proposed in your clinical trial protocol. This specification should be revised to be within the safety limits for endotoxin levels in the proposed dose.
- Similar comment for DNA content specification
  - **Pet Peeve #5 poor communication within your company (namely CMC, Reg Affairs and Clinical)**
  - **Pet Peeve #4 repeating mistakes (we have found this issue in multiple INDs from the same sponsors)**

Track/log comments for other products... never get dinged for the same item twice! - Joseph Kutza

Insufficient information

- Viral safety
  - Manufacturing scheme is validated for its ability to remove or inactivate retroviruses BUT:
    - Insufficient data provided to support generic/modular clearance
    - No data allowing reviewer to assess appropriateness of scale down models
- Lack of manufacturing information
  - The IND does not contain information on the manufacturing process used for production of the radiolabeled monoclonal antibody.
- Lack of sufficient stability data
  - The stability data submitted in the IND is for a different formulation than that of the clinical drug product
- Lack of sufficient comparison between toxicology and clinical lots
  - Provide data to support the comparability of non-clinical and clinical batches of your monoclonal antibody

Take Home Message #3 **Trust but verify**
Pet Peeve #2 **Poor Communication with FDA- *Incomplete details***
Pet Peeve #3 **Data Presentation - *Missing data***
Pet Peeve #6 **Back up your claims with data**

Insufficient information

- “The IND does not contain information on the manufacturing process used for production of the radiolabeled monoclonal antibody. Provide detailed..”
- “The stability data submitted in the IND is for a different formulation than that of the clinical drug product (DP). Stability data for the DP in its clinical formulation is required to support the use of mAb ABC in the proposed clinical trial ..”
- “Provide data to support the comparability of non-clinical and clinical batches of your monoclonal antibody”
- “The IND does not contain information on the country of origin of (ruminant or human derived materials) used in the manufacturing of mAb ABC”

Speedbumps to avoid with Endogenous Protein counterparts

- Immunogenicity assays
  - Should be in place by Phase 1
  - Testing of patient samples should start with Phase 1 trial
- Potency assays

  Seek most relevant and quantitative bioassay possible (flexibility regarding what is possible balanced with what is quantifiable)
- Assays to assess levels of aggregates
  - More stringent for allowable levels of aggregates (aggregates influence immunogenicity)

Phase 2 and 3 Speed Bumps

- For Phase 2 and 3, FDA's primary objectives include: "to help assure the **quality of the scientific evaluation of drugs is adequate** to permit an evaluation of the drug's effectiveness and safety". (21CFR312.22)
- CMC development should parallel clinical development.
- Product characterization assays should be adequately qualified.
- When modifying or adding a clinical protocol, remember to submit the associated CMC information.
  - Adding placebo controlled trial requires CMC information for the placebo
  - Adding another product in conjunction with your product requires CMC information or letter of cross-reference to the IND, BLA, NDA or DMF.
  - Adding a radiolabel to the product for imaging etc. requires CMC information for the radionuclide and for the radiolabeled protein. (May require a new IND)

Pet Peeve #2 **Poor Communication with FDA- *Incomplete details***
Pet Peeve #3 **Data Presentation - *Missing data***
Pet Peeve #6 **Back up your claims with data**

Phase 2 and 3 Speed Bumps

Change happens! and comparability is needed.

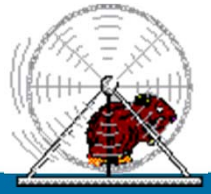
- Don't be left without the comparator product - assure sufficient retention of lots to support comparability studies.
- Establish and communicate pre-specified acceptance criteria
- Assure sufficient time to test for comparability and for FDA to review comparability data prior to use of new process material in clinical trial. **See Overarching Pet Peeves about pure fantasy**
- Have "plan B"- if processes 1 and 2 do not result in comparable products. You may need non-clinical or clinical cross over studies.

Pet Peeve #2 **Poor Communication with FDA- *Incomplete details***
Pet Peeve #3 **Data Presentation - *Missing data***
Pet Peeve #5 **Poor communication within your company**
Pet Peeve #6 **Back up your claims with data**

Case study - comparability

- During early phase 3 development of a monoclonal antibody, multiple manufacturing changes were made including:
  - removal of animal-derived raw materials from the process
  - new cell clone → new MCB and WCB.
  - Change in DS manufacturing site
  - Scaled up Bioreactors
  - Change to the harvest process and to the downstream operations
- IND amendment included a plan for comparability and introduction of product to the phase 3 trial.
- Plan did not adequately address ICH Q5a (viral safety) risks.
- Plan did not provide detailed acceptance criteria
- Plan did not provide any data on which one would base acceptance criteria.

Pet Peeve #2 **Poor Communication with FDA- *Incomplete details***
Pet Peeve #3 **Data Presentation - *Missing data***
Pet Peeve #6 **Back up your claims with data**



The BLA – Review: case studies

- Omission of key data from BLA resulted in delay of approval. Major amendments move the clock timeline.
- Drug Substance stability studies were conducted in containers not representative of the drug substance container material. Stability studies had to be redone, approved with shorter shelf-life
- Drug product long term stability data from pilot scale not representative of full scale. Resulted in a shorter expiration dating than requested.
- Request to drop specific release test for the "to be approved product" was not supported by sufficient information. BLA was approved on time, but sponsor had to include release test that they did not plan on and validate the assay during the BLA review cycle.

PDUFA V should help eliminate some BLA roadblocks, but it is up to you!

Roadblocks that may be identified at various times in product lifecycle

- Inspection
  - GMP, but also verifies that data in submission is accurate
- Contradictory/unclear statements within submission or between OS and amendments
- Key and critical process and product parameters lacking
  - Complex QbD submissions (Priority review)
- Clonality of MCB
- Unexpected adventitious agents
  - MMV, Cache Valley Virus, Vesivirus, Porcine circovirus-1, Leptospira

Breakthrough Therapy Designation

- Based on promising clinical results from early studies
- Accelerated clinical development program
- Product must still meet same quality standards as for product in full development program
- Consider market demand as well as your ability to supply ongoing clinical trials
- Plan CMC meetings during remaining clinical development program
  - Scale up
  - Comparability
  - Validation of process

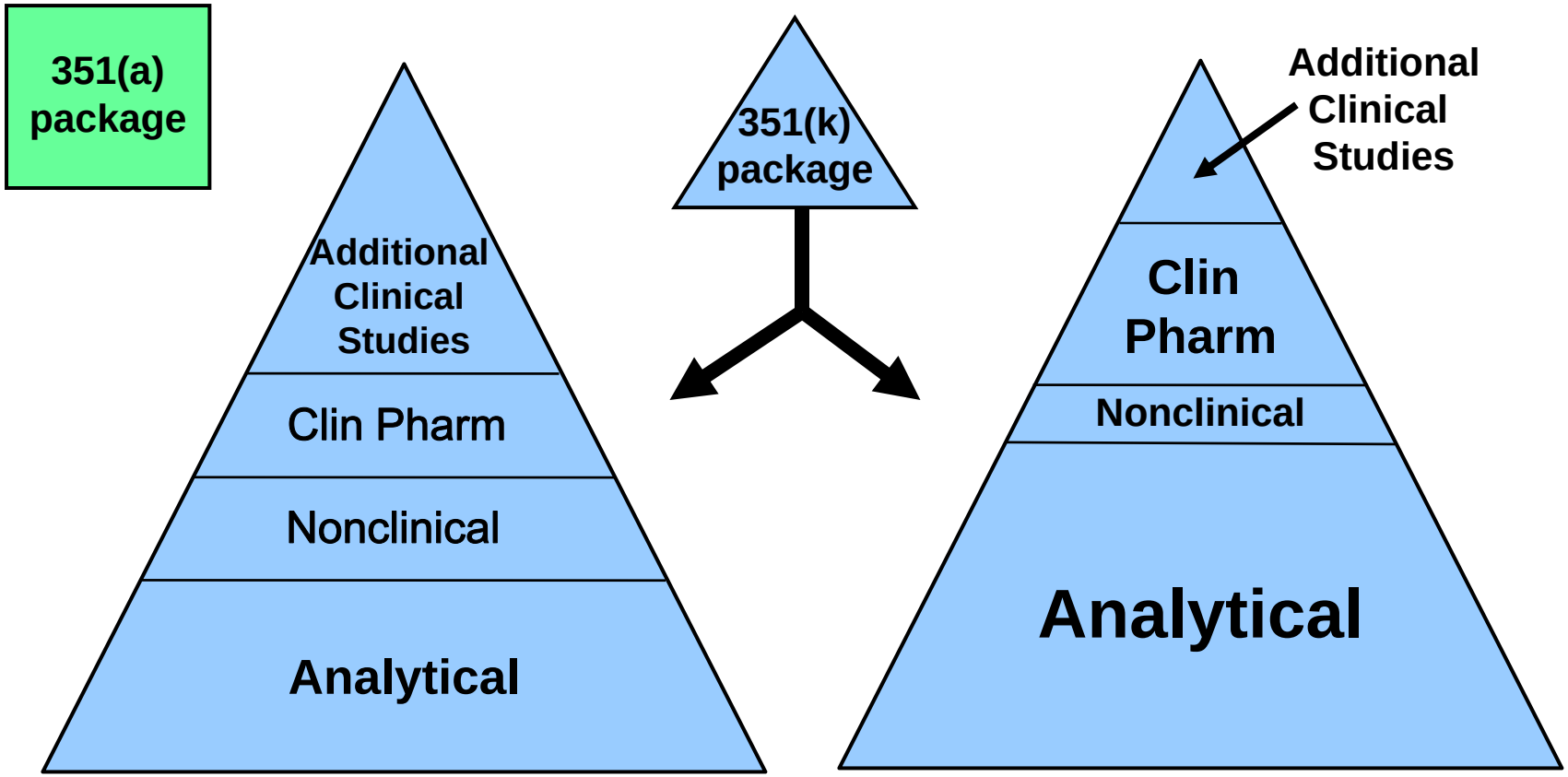
Biosimilar Product Development

Definition: Biosimilarity

Biosimilar or **Biosimilarity** means:

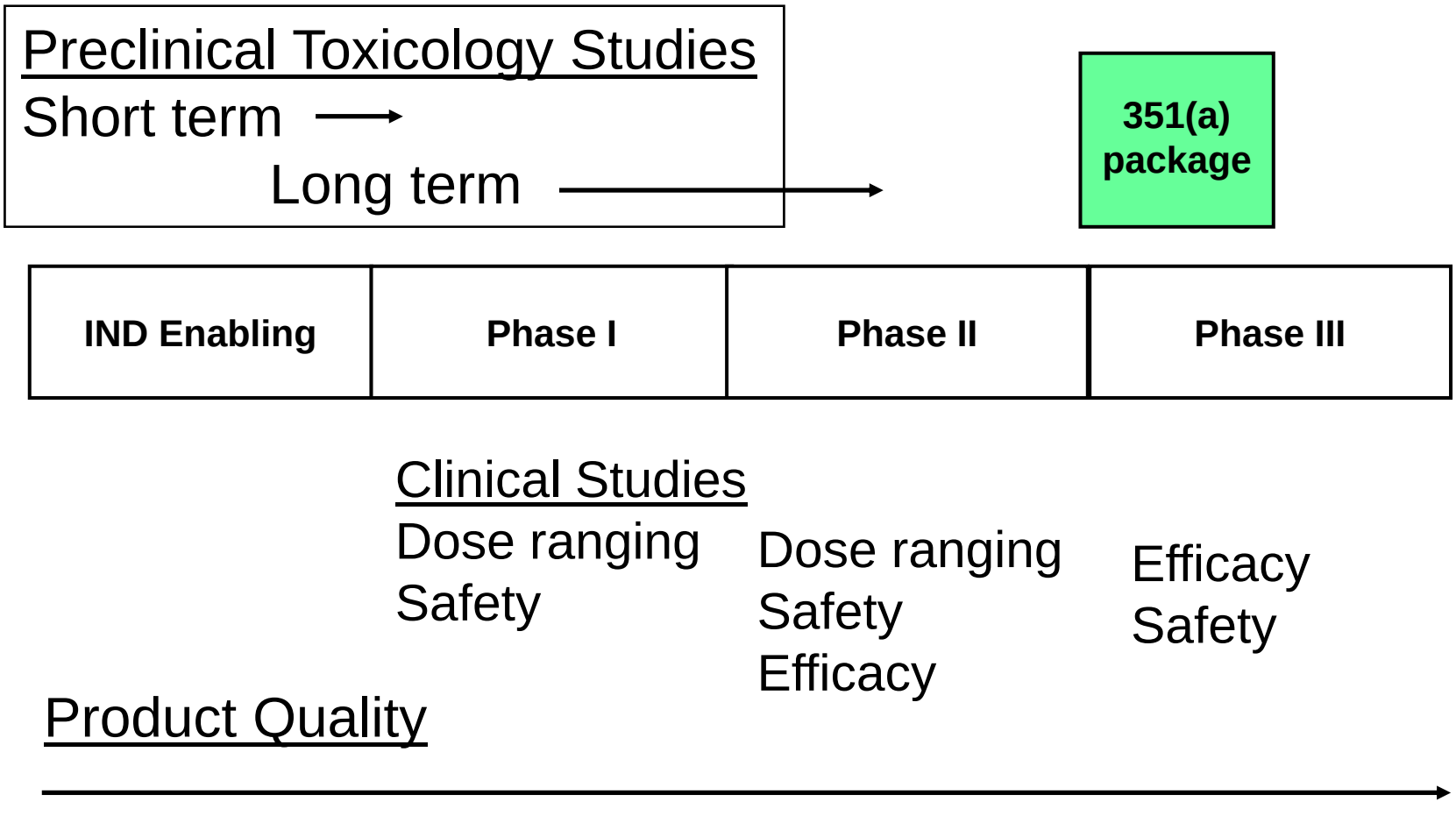
- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and
- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Highly Similar Analytical and PK/PD Data = Lower Risk of Clinical Differences

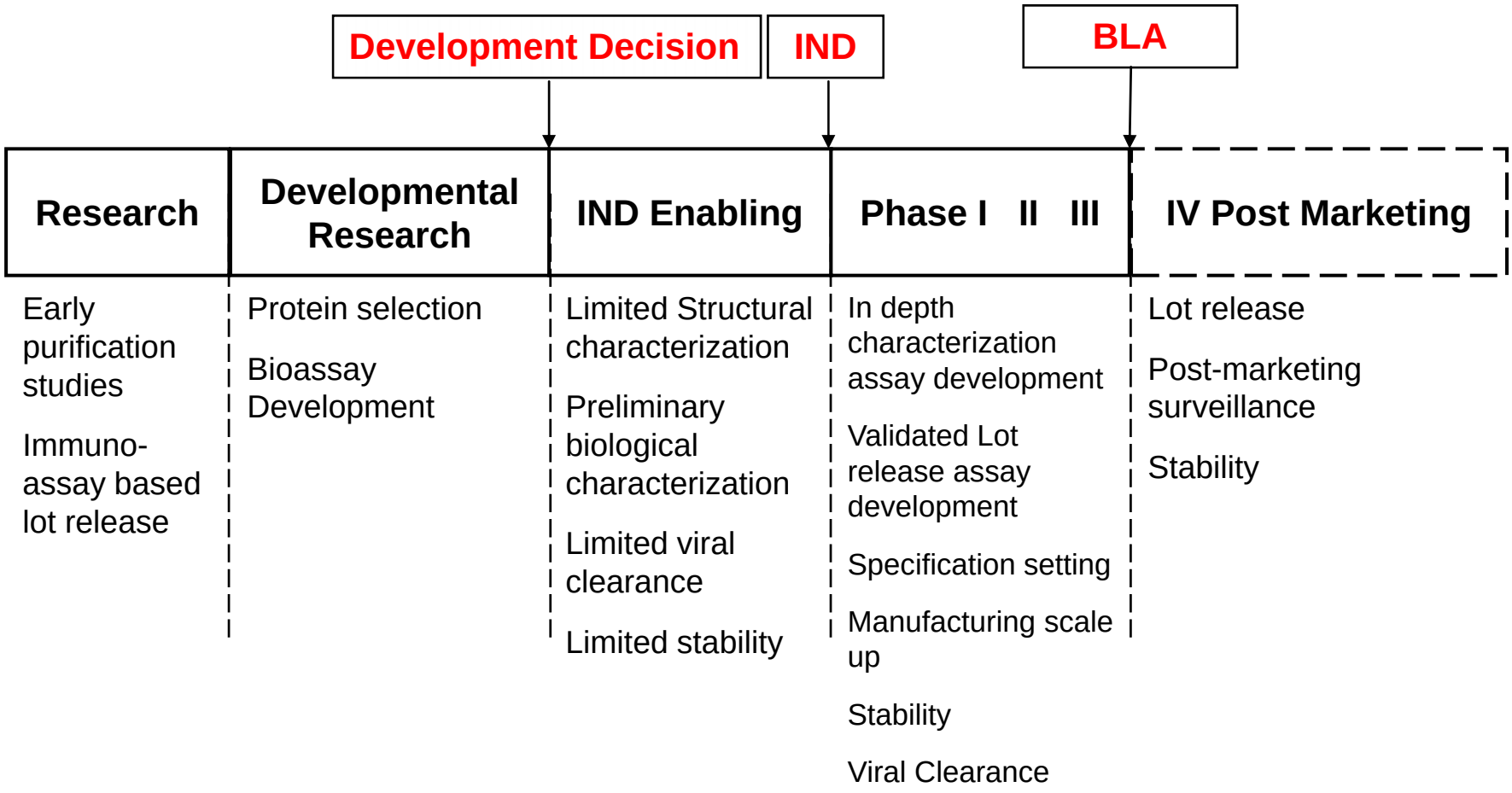


Two approaches to achieve biosimilarity

Data Collection During New Biological Entity Product Development



Product Quality Assays During New Biological Entity Product Development



Data Collection During Biosimilar Product Development

Preclinical Toxicology Studies
Short term ⟶

351(k) package

IND Enabling	Initial Clinical Studies	Additional Clinical Studies

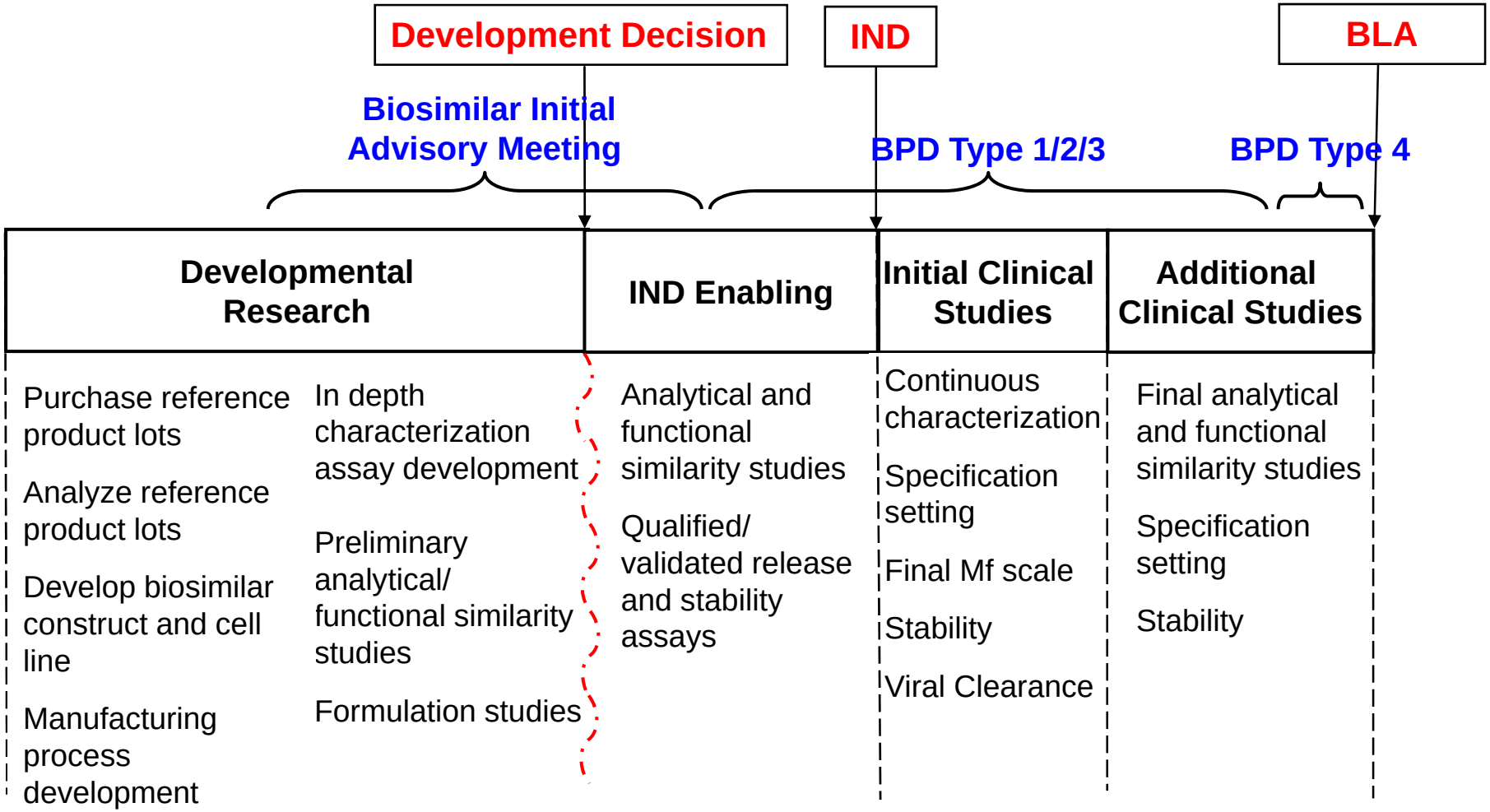
Clinical Studies
PK/PD

Immunogenicity
Additional Clinical Studies

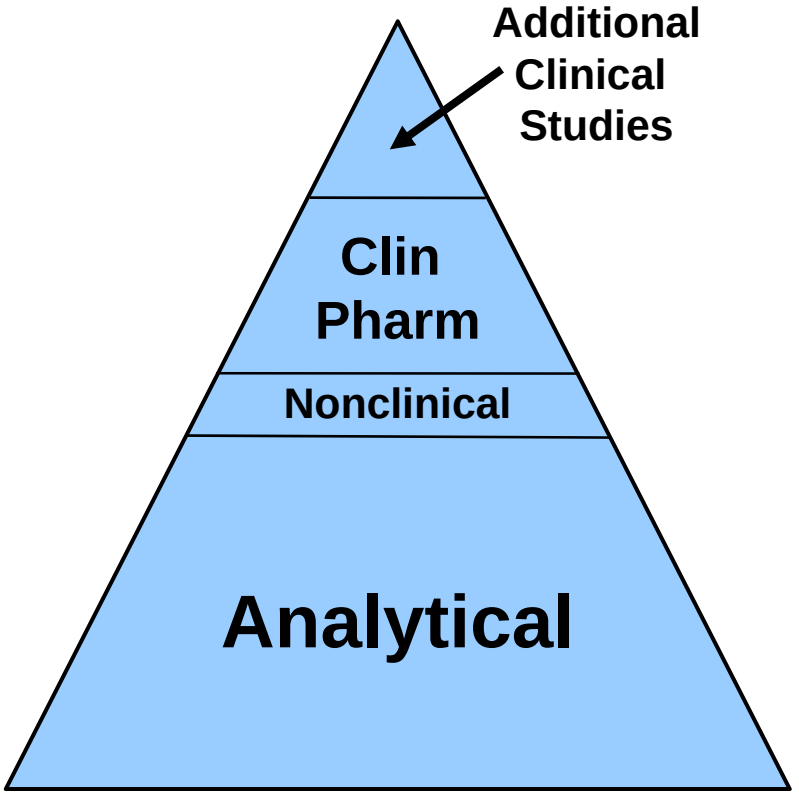
Product Quality

Depends on extent of analytical similarity and PK/PD similarity prior to this point

Preferred Biosimilar Product Quality Development Process



Quality as the Foundation



- It's not just the panel of methods and results
- Reliability of the methods
- Biosimilar product lots and number of lots
- US-licensed reference product and non-US comparator lots and number of lots
- Understanding process to produce product with consistent quality attributes
- Timing of submission during clinical development

Back to the basics

- Your reviewers are scientists that base their decisions on data analysis. So back up your claims with quality data!
  (Pet Peeves #3 & #6)
- The CTD format is here to say. It can work for you if you let it.
  (Pet Peeve #1)
- Communication is key – with FDA and within your companies.
  (Pet Peeves #2, #4 & #5)
- An open relationship based on trust and information sharing is the best relationship sponsors can have with their reviewers.
  (Take home message #3)

Acknowledgments

- All DMA and DTP colleagues who shared their pet peeves and examples – there were many!

FDA or Sponsor?

The BLA – Filing

- ✓ Filing review checks that:
  - All necessary information is contained in the BLA
    - **Incomplete details and Poorly written submission**
    - **Pet Peeve #2 Poor communication with FDA**
    - **Take Home Message #2 Substance with style**
  - Process validation is complete and included in the submission
  - BLA is well organized to enable review.
    - **Pet Peeve #1 - CTD format**
    - **Take Home Message #2 Substance with style**
  - Pre-approval/ Pre-license inspections:
    - All sites should be ready for inspection at time of submission
    - Expectation is that manufacturing of your protein takes place during inspection – plan accordingly, and inform FDA of your manufacturing schedule at time of BLA submission. 21CFR601.20(b)(2)

The BLA – Filing Roadblocks

- Sponsor wanted to provide DP process validation data for a format that was not the to be marketed format. Was cautioned that this could be a reason for RTF so sponsor validated the correct format for BLA submission.

- The manufacturing sites were not ready for inspection at time of BLA submission. BLA was withdrawn until sites were ready for inspection.

- There was no plan to manufacture the product during the BLA review timeline. When sponsor was cautioned that BLA will not be filed, manufacturing schedules were changed to comply.

The BLA – Filing roadblocks

- ***Non-existent or insufficient data in several sections of module 3.***
  - *Section 3.2.S.2.4 (Control of Critical Steps and Intermediates) does not identify all process parameters per unit operation*
  - *Section 3.2.S.2.5 (Process validation and evaluation) is missing information such as: proven acceptable ranges and supporting data per unit operation, validation reports per unit operation, validation of buffers and media hold times, validation of bulk drug substance freezing process, chromatography resin cleaning validation, UF/DF validation report or a validation protocol if concurrent validation is to be performed*
  - *Section 3.2.S.4 (Control of Drug Substance) does not have qualification/validation data for the following methods used for release and/or stability of DS*

The BLA – Filing roadblocks

- ***Non-existent or insufficient data in several sections of module 3.***
  - *The submission does not contain information on the process and controls for the packaging and labeling of the vialed DP by the manufacturing sites listed in the BLA.*
  - *Multiple links are not operational throughout the BLA. For example…*
  - *Appendices and special sections are difficult to navigate due to lack of granularity.*

The BLA – Communicating with FDA

- When is a good time to tell FDA that your facility has not been able to manufacture lots post validation because (bioburden, unknown contaminant, viral contamination, other)?
  - Develop a trust-based relationship
  - Be upfront with the circumstances surrounding unusual issues (reprocessing, reworking, relabeling, OOS's etc).
- **Remember take home message #1 about grumpy reviewers.**
  - The way to keep your reviewer happy is to be open, truthful, and provide the information needed for review and assessment of your process and product.
- Lower quality submissions may be more likely to miss a PDUFA date
  - Multiple rounds of questions and requests for information
  - Post-marketing commitments may be required

More on Biosimilars

Biosimilar User Fee Act of 2012 (BsUFA)

- BsUFA authorizes FDA to assess and collect fees for biosimilar biological products from October 2012 through September 2017
  - Fees support FDA's biosimilar review program activities
  - BsUFA fee rates are set equal to PDUFA fee rates for applications, supplements, establishments, and products
  - BSUFA also includes biosimilar biological product development (BPD) fees for products in the development phase.
    - When a sponsor submits a biosimilar biological product application for a product, the fee for the application is reduced by the cumulative amount of previously paid BPD fees for the product
- FDA committed to review performance goals under BsUFA
  - BsUFA goal types are similar to the PDUFA goal types, with some differences in timeframes
  - Under the BSUFA program, there are five types of formal meetings that can occur between sponsors and FDA staff to discuss biosimilar development programs
- http://www.fda.gov/bsufa

Biosimilar Product Development Meetings

BPD Type 1 Meeting: a meeting which is necessary **for an otherwise stalled drug development program** to proceed (e.g. special protocol assessment meeting, meeting to discuss clinical holds, dispute resolution meeting) or to address an important safety issue.

BPD Type 2 Meeting: a meeting to **discuss a specific issue** (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing biosimilar biological product development program. Such term includes **substantive review of summary data, but does not include review of full study reports**.

BPD Type 3 Meeting: an in **depth data review** and advice meeting regarding an ongoing biosimilar biological product development program. Such term **includes substantive review of full study reports**, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding additional studies, including design and analysis.

BPD Type 4 Meeting: a meeting to discuss the **format and content** of a biosimilar biological product **application or supplement** submitted under 351(k) of the PHS Act.

Q&A Guidance: Revised Definition of a "Biological Product"

- BPCI Act amends the statutory definition of "biological product" to include a "protein (except any chemically synthesized polypeptide)."

- FDA has developed the following interpretation of the statutory terms "Protein" and "Chemically synthesized polypeptide."

  – Protein: Any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

  – Chemically synthesized polypeptide: Any alpha amino acid polymer that
    1. is made entirely by chemical synthesis; and
    2. is less than 100 amino acids in size.

- An application for a "biological product" must be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period that ends March 23, 2020.